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EXAMINER
SCHEINER, L

ART UNIT	PAPER NUMBER
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DATE MAILED: 04/05/91

STEVEN M. ODRE, ESQ.
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This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 1/7/91 ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-39 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-39 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev.9-89)

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Mullis et al in view of Carr and Whiteley et al for reasons of record.

Claims 1-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Carr and Whiteley et al in view of Mullis et al for reasons of record.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the

> invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

It is noted that the specification, at page 15, teaches that where heat denaturation is used, it is preferred to use a thermostable ligase. Because heat denaturation is required in all instant examples, the thermostable enzyme is essential to the claimed invention. The enzyme must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the enzyme is not so obtainable or available, the requirements of 35 U.S.C. 112 may be satisfied by a deposit of the organism from which the enzyme is obtained. The specification does not disclose a repeatable process to obtain the enzyme and it is not apparent if the enzyme is readily available to the public. It is noted that applicants have not deposited the enzyme source and there is no indication in the specification as to the public availability. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or by a statement by an attorney of record, stating that the specific strains have been deposited under the Budapest Treaty and that the strains will be

irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. Also, because the deposit was not made at or before the time of filing the instant application, a chain of custody is also required.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in MPEP 608.01 (p)(c), applicants may provide assurance of compliance by a affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting the patent;

(c) the deposits will be maintained in the public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

(d) the deposits will be replaced if it should ever become inviable.

Claims 3, 11, 17 and 39 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-39 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited

to Escherichia coli DNA ligase. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Enablement must be commensurate with the scope of the claims. In complex or unexplored art guidance is needed to avoid undue experimentation. Applicant's attention is directed to In re Colianni, 195 USPQ 150, (1972). Only the use of E. coli DNA ligase has been disclosed as a means of ligating hybridized amplification probes and it would have required one of ordinary skill in the art an undue amount of experimentation to have found another enzyme that would have functioned in the assay as claimed.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-39 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a target nucleic acid sequence wherein the nucleotide sequence is known (or the putative sequence has been determined). See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-39 are not enabled for "a target nucleic acid sequence" or "amplification sequence" because one would not know what synthetic oligonucleotide sequence (amplification probes) to

generate and it would be critical that the probes were 100% homologous to template in order to maintain the integrity of sequence following repeated cycling.

Claims 1-39 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Functional language should be recited in claims regarding relative probe length and also the length of one probe relative to the others as the limitations of the specification must be read into the claims. However, the specification does not teach probe length or relative probe length and is therefor not enabling for a plurality of denatured pairs of amplification probes. As probe number and respective lengths are critical to the hybridization reaction as it is both individual probe length, relative probe length, and excess concentration of probe that will "drive the reaction forward".

Applicants argue that there is no teaching or suggestion in the prior art which would lead one to combine Mullis with Carr and/or Whiteley et al. According to applicants the latter two references are directed to analytical methods which do not contemplate amplification. Examiner contends that the test of obviousness is not express suggestion of the claimed invention in

any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them. Applicants' attention is directed to In re Rosselet, 146 USPQ 183, 1965. Applicants failure to consider the references together by stating that Carr and Whiteley et al do not contemplate amplification is inappropriate in view of the fact that the rejection was made under 35 U.S.C. 103, on the basis of what the combined teachings of the references would have suggested to one of ordinary skill in the relevant art, and not under 35 U.S.C. 102, on the basis of anticipation by any of the individual references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA); In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968). Again, one of ordinary skill in the art presumed to be familiar with the applied references would know that what was important was the formation of the complementary sequence and that whether one used short fragments (amplification probes) of DNA and a polymerase or short fragments of DNA and a ligase with or without a polymerase that the only thing of importance was the formation of a complementary strand which could be used in subsequent reactions as taught collectively by Mullis et al, Carr and Whiteley et al.

Applicants argue that their method allows the blunt-end by-product formed and instead discriminates the non-target-derived blunt-end ligated product from the desired amplification product. They further state that by employing their unique detection

system, incorrectly aligned spurious blunt-end ligated amplification by-product cannot act as a template for hybridization of the detection probes. As a result, the detection product serves as an indication of only the correctly assembled amplification product, nearly all of which is traceable to the presence of the target.

Examiner argues that the background caused by target independent ligation of non-hybridized probes can defeat the entire purpose of the amplification procedure by masking results from samples at the sensitivities which require target amplification in the first place and is not prevented by the instant method in any way. Examiner contends that Whiteley et al clearly teach that which applicants argue is their unique method of discriminating against incorrectly assembled amplification product. By increasing the number of probes (3 or more) applicants simply statistically reduce the likelihood that correctly aligned amplification product in the absence of target sequence is formed. Their method does not, however, decrease the occurrence of spurious by-product. Thus, applicants' method as claimed does not appear to address the problem of background caused by incorrectly aligned spurious blunt-end ligated amplification by-product.

Applicants state that their detection product serves as an indication of only the correctly assembled amplification product, nearly all of which is traceable to the presence of target.

Examiner is confused by this statement because 1) any system employing a specific probe is capable of detecting correctly assembled target or amplification product as long as respective probe sequences are specific for the aligned fragment junctions, and 2) the statement seems to imply that one can quantitatively determine how much target existed in the original sample. However, the argument appears to be faulty because if the correctly aligned spurious blunt-end ligated amplification by-product (low copy number) was formed early in the cycling and subsequent exponential amplification occurred there would be just as much if not more product produced from target-independent ligated by-product than from original target of interest.

Applicants state that it is only critical that the probes have sufficient complementarity to enable hybridization to occur.

Examiner contends that maybe some other method only requires sufficient complementarity, however, applicants claim a ligation amplification method and not a method for geometric amplification of mutant target sequence. In other words, the specification is only enabled for the amplification of a single target sequence of interest and not amplification of multiple random mutations.

Applicants' remarks regarding probe length and excess concentration are not at all convincing because the arguments address a single probe length or overall length of the contiguously hybridized amplification probe and not relative lengths of the three or more individual pairs of probes prior to

the ligation reaction, as claimed. Applicants arguments have been considered but are not convincing.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Laurie Scheiner at telephone number (703) 308-3990.

CHRISTINE NUCKER
PRIMARY EXAMINER
ART UNIT 187

LAS

Laurie Scheiner
April 2, 1991